

Remarks

In the Advisory Action, it is indicated that claim amendments submitted in Applicants' Response dated June 8, 2006 were not entered. Accordingly, Applicants herein provide claim amendments substantially identical to those previously provided,¹ and respectfully request that these amendments be entered into the records of this application.

Claims 24, 26-31, and 33-35 are pending in this application upon the entry of the amendments provided herein. Claims 24, 29 and 31 are amended to recite "pregelatinized corn starch." Support for the amendments can be found, for example, on page 5, lines 5-11, page 11, lines 12-18, and page 16, Table 2 of the specification. Claim 26 is amended to correct its dependency. No new matter has been added.

Applicants respectfully submit that all of the pending claims are allowable for the following reasons.

A. The Objection to Claims Under 35 U.S.C. § 132(a) Should Be Withdrawn

On page 2 of the Office Action, the claim amendments made in Applicants' previous response are objected to under 35 U.S.C. § 132(a) for allegedly introducing a new matter. In particular, it is alleged that the term "direct blend" is not "defined or even disclosed in the specification." (Office Action, page 2).

Although Applicants respectfully disagree, especially in view of the fact that a detailed exemplary process for making the compositions of this invention is described on page 13 of the specification², the claims are amended to recite, in part, a composition comprising a uniform admixture of thalidomide and pregelatinized corn starch, as suggested by the Examiners during the interview held on June 6, 2006. In view of these amendments, Applicants respectfully request that the rejection of the claims under 35 U.S.C. §132(a) be withdrawn.³

¹ The only difference is that claim 26 is amended in this paper to correct its dependency.

² It should be noted that sections 4.2.1-4.2.5, with the exception of section 4.2.3, describe the direct blend process which does not involve roller compaction. Although section 4.2.3 describes the roller compaction process, it is clearly provided that the roller compaction is an optional process ("the pre-blend may be passed through a roller compactor").

³ Indeed, the Examiner indicates in the Advisory Action that the rejection would have been overcome if the amendments provided in the June 8, 2006 Response had been entered. (Advisory Action, page 2).

2. The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 3-8 of the Office Action, the claims were rejected as allegedly obvious over various references. According to the suggestions made by the Examiner in the Office Action, and during the June 6th interview, claims 24, 29, and 31 are amended to recite, in part, the specific excipient “pregelatinized corn starch.”⁴ In addition, Applicants submitted in their June 8th Response a copy of “Starch, Pregelatinized,” *Handbook of Pharmaceutical Excipients*, 3rd Ed., pp. 528-530 (2000), which is a well-known textbook concerning pharmaceutical excipients, to show that no excessive variation exists as to the scope of the term. Such was required by the Examiner.

In the Advisory Action, however, the Examiner requests that the following further evidence be provided: 1) the detailed information of the formulations used in the bioavailability data previously submitted (Advisory Action, page 2); 2) showing of a comparison of properties between thalidomide formulations containing the same amount of different carriers (*id.*, page 4); and 3) showing of a long-felt need for thalidomide formulations in smaller capsule sizes (*id.*). Applicants herein provide the requested information.

First, the formulations used in the bioavailability studies have the following ingredients:

Formulation	Formulation designated “Original 50 mg” in Table 6.36	Formulation designated “New 50 mg” in Table 6.36	Formulation designated “New 200 mg” in Table 6.37
Ingredients	Thalidomide 50 mg Microcrystalline cellulose 60 mg Kollidon 90F 12 mg Stearic acid NF 4 mg Colloidal silicon dioxide 0.8 mg Crospovidone 16 mg Lactose 257.3 mg	Thalidomide 50 mg Pregelatinized corn starch 74 mg Magnesium stearate 1 mg	Thalidomide 200 mg Pregelatinized corn starch 297.5 mg Magnesium stearate 2.5 mg
Total	400 mg	125 mg	500 mg
Capsule Size	Size 0	Size 4	Size 0

As this information will make it clear, “new 50 mg” thalidomide formulation, despite having been formulated in a much smaller capsule size with much

⁴ Applicants still respectfully disagree with the contention that claims reciting specific amounts of thalidomide and carrier in a specific capsule size are obvious over the references cited by the Examiner. (See Applicants’ June 8 Response, pages 7-8). In this regard, Applicants wish to note on the records that the amendments made herein are presented solely to expedite the prosecution of this application. All rights are reserved.

lower amount of excipients, exhibited bioavailability equivalent to that of “original 50 mg” formulation. (See Exhibit A to Applicants’ Response dated December 7, 2005, Table 6.36). Similarly, “new 200 mg” thalidomide formulation exhibited bioavailability equivalent to that of four capsules of “new 50 mg” formulation, and thus, to that of four capsules of “original 50 mg” formulation. (*Id.*, Table 6.37).

Second, it is alleged that Applicants’ assertions regarding flow-characteristics of thalidomide formulations are not supported by any factual basis. (Advisory Action, page 4). Thus, it is requested that showing of comparison of properties between formulations containing the same amount of different excipients be provided. (*Id.*). In this regard, Applicants provide the following information.

As pointed out in their previous responses, the challenges surrounding the development of the claimed thalidomide formulations stemmed from the fact that, due to the limitation as to the amount of excipients that can be used, it was difficult to make a formulation with acceptable flow-characteristics as well as the required bioavailability. In view of those considerations, several excipients, whose densities may be sufficiently high to allow for the contemplated formulations, were selected and studied. The following formulations represent a few of the experimental blends, which were studied further:

Blends	A		B		C	
Ingredients (in w/w percent)	Thalidomide	40	Thalidomide	40	Thalidomide	40
	Pregelatinized		Colloidal silica	0.5	Sodium starch	
	corn starch	59.5	DC lactose	59	glycolate	5
	Magnesium		Magnesium		Dextrates	54.5
	stearate	0.5	stearate	0.5	Magnesium	
					stearate	0.5

The tap densities of the above blends were determined, and their flow-characteristics were also determined using Flo-disc device. It should be noted that values higher than 20 mm, as determined using the Flo-disc, are generally considered to be poor. The tap densities and flow-characteristics of those blends so determined are summarized below:

Blends	A	B	C
Tap Density	0.78	0.74	0.83
Flo-Disc (mm)	16	14	26

As can be seen from the above, Blend C exhibited poor flow-characteristics. Further, although Blend B exhibited acceptable flow-characteristics, the tap density was not sufficient to allow for filling at the 200 mg strength into a size 0 capsule. On the other

hand, Blend A (the claimed formulation) exhibited both good flow-characteristics and sufficiently high tap density. Therefore, these results show that while Blends B and C contained the same amount of certain other excipients, their properties were not suitable to fit the contemplated formulations, and thus, clearly evidence that the claimed formulation possesses superior properties over the formulations provided herein, which contain the same amount of certain other excipients.

Finally, it is requested that showing of “long-felt need” for the claimed thalidomide formulations be provided. In this regard, Applicants submit herewith a copy of *Biologics*, vol. 3, issue 6 (2003), available from www.biologics.today.com (“*Biologics*”), attached hereto as **Exhibit A**. As the Examiner will see, *Biologics* provides that Celgene Corporation (the assignee of the current application) shrunk thalidomide capsule sizes and states that the “new capsule is about half the size of the original product and *should be easier for patients to swallow.*” (*Biologics*, second page) (emphasis added). The fact that an industry magazine found the reduction of the capsule size newsworthy clearly indicates that the problems associated with having to swallow large size capsules of thalidomide were well-recognized in the art.

Furthermore, Applicants also submit copies of abstracts from Singhal *et al.*, *New England Journal of Medicine*, 341(21): 1565-1571 (1999), attached hereto as **Exhibit B**, and Figg *et al.*, *Journal of Pharmaceutical Science*, 88(1): 121-125 (1999), attached hereto as **Exhibit C**. As the Examiner will see, these references show that doses of thalidomide from 200 mg to over 1000 mg were routinely given to patients. This means that the patients would have required to take 4 to over 20 of the then-available thalidomide capsules (50 mg thalidomide in size 0 capsules). Therefore, there would be little question that patients would have had difficulties, in addition to tremendous inconvenience and discomfort, swallowing the required number of the large-sized capsules.

In sum, Applicants again respectfully point out that the claimed formulations, which contain higher amount of thalidomide than the formulation known at the time of this application, but have the same capsule size⁵, and yet is bioequivalent to the known thalidomide formulation, would not have been obvious over the references cited by the Examiner. Applicants previously submitted, or herewith submit: 1) the showing of bioequivalency between the claimed formulation and the formulation known at the time of this application, with the detailed description of the ingredients for each of the formulations; 2) the showing of superior flow-characteristics of the claimed formulations as compared

⁵ Or contain the same amount of thalidomide as the known formulation, but have a smaller capsule size.

with other formulations containing the same amount of other excipients; and 3) evidence that "long-felt need" indeed existed in the art prior to this invention. In view of the above, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

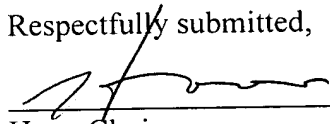
Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and respectfully request that the rejection of the pending claims be withdrawn.

No fee is believed due for the submission of this paper. If any fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Date: December 4, 2006

Respectfully submitted,



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Exhibit A

Survey nets positive feedback from nurses

Biologics is pleased to share some of the responses we've received so far from a recent survey of oncology nurses about our services.

Thank you to all of the nurses who so kindly took the time to respond to our survey. We have had an incredible response and appreciate the feedback. We are still happily receiving replies.

- 99% said Biologics saves time during their day
- 98% said Biologics provides a higher level of comfort than a retail pharmacy.

We very much appreciate the written comments which include:

"We think you are fantastic. The services to our patients have helped many people who feel they are in a helpless situation. Thanks for everything."

"Y'all are wonderful! You make things so much easier for the patient. Kudos!"

"We love working with Biologics. They best suit the needs of the team and the patients."

"Biologics continues to offer excellent service. It is a definite plus for our patients."

"I love the service provided. It is great dealing with professional people."

"I have been pleased with your service."

"Most of the prescriptions are called in by the physicians. However, I have had to do the same at times. Your verification of dosages and height and weights are good as well. The patients are happy with your services."

And our favorite, in response to the pens we provided with the survey

"Click pens are better than pens with caps."

(There's always room for improvement.)

Q&A with Dr. Henry Friedman:

Optimism at heart of brain tumor treatment strategy

Oncology Today is honored to have Henry S. Friedman, M.D., Co-Director, The Clinical Neuro-Oncology Program at The Brain Tumor Center at Duke share his insight on his career, Duke and treatment strategies. The Biologics team is honored to have the opportunity to care for many of Dr. Friedman's patients.

OT: What made you decide on a career in neuro-oncology?

Dr. Friedman: In 1980, I was training in Syracuse in Pediatric Hematology-Oncology. Although I was working in a hematology research lab at that time, my heart was set on doing oncology research. When I told that to my program head, Dr. Frank Oski, he told me if I was going to work in oncology, I should work in neuro-oncology because there was a total lack of progress in the field because few people are working on this problem. Subsequently when I moved to Duke in July of 1981, I decided to follow his advice and entered the laboratory of Dr. Darell Bigner and trained in neuro-oncology.

OT: How do you feel about the level of national recognition you have earned during your career?

Dr. Friedman: I am gratified to be well-respected in my field because it means, at least in theory, that I am making contributions that are important to neuro-oncology. I believe that I have helped in several ways including developing new strategies for the treatment of patients with brain tumors and also focusing on the importance of patients seeking optimistic therapy rather than settling for treatment strategies proven to be ineffective.

OT: Is there one particular treatment that gives you hope as a doctor?

Dr. Friedman: I do not believe there is any one particular treatment that will prove to be the single magic bullet in the treatment of brain tumors. The strategies that I believe will prove to be important include regional therapy such as convection enhanced delivery, monoclonal antibody delivery of radioisotopes or toxins, vaccine therapy, small molecule inhibitors and strategies to understand why current agents fail and how one can restore sensitivity to them.

OT: Is there one incident that occurred that really solidified your decision to be a neuro-oncologist?

Dr. Friedman: I never forgot what Dr. Frank Oski told me when I wanted to switch from hematology to oncology research. When I went to Duke, the opportunity was presented to work in any number of different research fields. I immediately remembered his words and chose to focus on brain tumor research.

OT: If there is one bit of advice you could offer to all brain tumor patients, what would it be?

Dr. Friedman: The best advice that I could give would be for all patients to be sure they are offered hope. If a physician tells you that it is hopeless and nothing can be done or that strategies have been proven to be ineffective, seek an opinion elsewhere. Although it is true that many patients with brain tumors die, the only ones who survive are those who were treated in an optimistic, hope-filled fashion.

OT: What is unique about the Brain Tumor Center at Duke?

Dr. Friedman: The Brain Tumor Center at Duke is unique because it embraces a seamless transition between basic laboratory research to pre-clinical research to clinical research. We wed this research effort to extremely strong clinical and quality-of-life teams.

OT: When you're not working, how do you spend your time?

Dr. Friedman: My life is quite simple and revolves around family, The Brain Tumor Center at Duke and basketball. I attend all of the Duke Men and Women's basketball games and of course all of my daughter's high school and AAU basketball games. I am one of the managers of her AAU team and am constantly involved with these committed young women. I have been married to Dr. Joanne Kurtzberg since 1981. Joanne is the head of the Pediatric Stem Cell Program and one of the world's leaders in her field. I have a son, Joshua, who is 20 and just finishing his sophomore year at Duke and a daughter, Sara, who is 15 and just finishing her freshman year in high school.

Facts about The Brain Tumor Center at Duke:

- Currently cares for more than 1,000 patients with brain tumors—pediatric and adult—who have come to Duke from all over the world.
- Houses one of three brain tumor research programs recognized by the National Institutes of Health.
- Offers more active clinical trials than any other known treatment center.
- Nationally acclaimed Brain Tumor Family Support Center is the model for hospital-based support programs throughout the United States.

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Lipogene shrinks Thalomid 50mg capsules

Lipogene, a leading manufacturer of specialty pharmaceuticals, has announced that it has received approval from the U.S. Food and Drug Administration (FDA) for a new, smaller size of Thalomid 50mg capsules. The new capsules are designed to be more comfortable to swallow and are available in a blister pack for convenience.

From the annals, marketing of the American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) has announced that it has received approval from the U.S. Food and Drug Administration (FDA) for a new, smaller size of Thalomid 50mg capsules. The new capsules are designed to be more comfortable to swallow and are available in a blister pack for convenience.

Thalomid 50mg capsules are used to treat multiple myeloma, a type of cancer that affects the bone marrow. The capsules are taken orally and are available in a blister pack for convenience.

Thalomid 50mg capsules are also used to treat other types of cancer, including breast cancer, lung cancer, and colorectal cancer. The capsules are taken orally and are available in a blister pack for convenience.

Biologics offers discounted cash price for Xeloda (capecitabine)

Biologics offers a discounted cash price for Xeloda (capecitabine) for patients who do not have health insurance coverage. The price is \$34.50 per capsule and \$500mg, 624.50 per capsule.

AWP: \$34.50

Biologics offers a discounted cash price for Xeloda (capecitabine) for patients who do not have health insurance coverage. The price is \$34.50 per capsule and \$500mg, 624.50 per capsule.

Biologics offers discounted cash price for Xeloda (capecitabine)

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AWP: \$34.50 per capsule and \$500mg, 624.50 per capsule

Biologics cash price: AWP - 45% = \$34.50 dispensing fee

Counseling by phone effective with patients

Counseling by phone is an effective way to provide patient education and support. It allows patients to ask questions and receive answers from a healthcare professional without the need for a physical visit. This can be particularly helpful for patients who are unable to travel or who have busy schedules.

Research has shown that counseling by phone can lead to improved patient adherence and better health outcomes. It can also help to reduce healthcare costs by preventing unnecessary hospitalizations and emergency room visits.

When counseling by phone, it is important to ensure that the patient is able to hear and understand the information being provided. It is also important to document the counseling session and to follow up with the patient as needed.

Biologics offers a discounted cash price for Xeloda (capecitabine) for patients who do not have health insurance coverage. The price is \$34.50 per capsule and \$500mg, 624.50 per capsule.



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☐ 1: N Engl J Med. 1999 Nov 18;341(21):1565-71.



Links

Erratum in:

N Engl J Med 2000 Feb 3;342(5):364.

Comment in:

N Engl J Med. 1999 Nov 18;341(21):1606-9.

N Engl J Med. 2000 Mar 30;342(13):975; author reply 975-6.

N Engl J Med. 2000 Sep 28;343(13):972-3.

N Engl J Med. 2001 Jun 21;344(25):1951-2.

Antitumor activity of thalidomide in refractory multiple myeloma.

Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, Munshi N, Anaissie E, Wilson C, Dhodapkar M, Zeddis J, Barlogie B.

Myeloma and Lymphoma Program, South Carolina Cancer Center, University of South Carolina, Columbia, USA.

BACKGROUND: Patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease. **METHODS:** Eighty-four previously treated patients with refractory myeloma (76 with a relapse after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days (range, 2 to 465). The starting dose was 200 mg daily, and the dose was increased by 200 mg every two weeks until it reached 800 mg per day. Response was assessed on the basis of a reduction of the myeloma protein in serum or Bence Jones protein in urine that lasted for at least six weeks. **RESULTS:** The serum or urine levels of paraprotein were reduced by at least 90 percent in eight patients (two had a complete remission), at least 75 percent in six patients, at least 50 percent in seven patients, and at least 25 percent in six patients, for a total rate of response of 32 percent. Reductions in the paraprotein levels were apparent within two months in 78 percent of the patients with a response and were associated with decreased numbers of plasma cells in bone marrow and increased hemoglobin levels. The microvascular density of bone marrow did not change significantly in patients with a response. At least one third of

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Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. [Br J Haematol. 2000]

Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma. [Haematologica. 2002]

Thalidomide in patients with advanced multiple myeloma: a study of 83 patients--report of the Intergroupe Francophone du Myelome (IFM). [Hematol J. 2002]

Consolidation therapy of multiple myeloma with thalidomide-dexamethasone after intensive chemotherapy. [Ann Oncol. 2002]

Discordant response or progression in patients with myeloma treated with thalidomide. [Leuk Lymphoma. 2004]

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the patients had mild or moderate constipation, weakness or fatigue, or somnolence. More severe adverse effects were infrequent (occurring in less than 10 percent of patients), and hematologic effects were rare. As of the most recent follow-up, 36 patients had died (30 with no response and 6 with a response). After 12 months of follow-up, Kaplan-Meier estimates of the mean (+/-SE) rates of event-free survival and overall survival for all patients were 22+/-5 percent and 58+/-5 percent, respectively. **CONCLUSIONS:** Thalidomide is active against advanced myeloma. It can induce marked and durable responses in some patients with multiple myeloma, including those who relapse after high-dose chemotherapy.

PMID: 10564685 [PubMed - indexed for MEDLINE]

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☐ 1: J Pharm Sci. 1999 Jan;88(1):121-5.



Links

Pharmacokinetics of thalidomide in an elderly prostate cancer population.

Figg WD, Raje S, Bauer KS, Tompkins A, Venzon D, Bergan R, Chen A, Hamilton M, Pluda J, Reed E.

Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Building 10, Room 5A01, 9000 Rockville Pike, Bethesda, Maryland 20892, USA. wdfigg@helix.nih.gov

Thalidomide, a glutamic acid derivative, has recently been shown to inhibit in vitro angiogenesis, the process of formation of new blood vessels. This Phase II study examined the pharmacokinetics of thalidomide in patients with clinically progressive hormone-refractory prostate cancer. Patients (aged 55 to 80 years) were randomized to two different arms, low dose versus high dose. Patients in the low-dose group were given 200 mg of thalidomide and patients in the high-dose group received 200 mg of thalidomide, with subsequent dose escalations to 1200 mg. Serial serum or blood samples were obtained for pharmacokinetic assessment after administration of a single oral dose or multiple daily dosing of thalidomide and were assayed by reversed-phase HPLC. Pharmacokinetic parameters for both the single and multiple dosing were calculated with ADAPT II. A one-compartment model best fit the data. After single dosing, the oral clearance and apparent volume of distribution for the low-dose regimen (n = 13) were 7.41 +/- 2.05 L/h and 66.93 +/- 34.27 L, respectively, whereas for the high-dose regimen (n = 11), these values were 7.21 +/- 2.89 L/h and 165.81 +/- 84.18 L, respectively. The elimination half-lives for the low and high dose were 6.52 +/- 3.81 and 18.25 +/- 14.08 h, respectively. After the multiple dosing of thalidomide, the oral clearance and apparent volume of distribution for the low-dose group (n = 10) were 6.35 +/- 1.64 L/h and 64.63 +/- 23.20 L, respectively, whereas for the high-dose group (n = 11), these values were 7.73 +/- 2.27 L/h and 167.85 +/- 82.08 L, respectively. The elimination half-lives for the low and high dose were 7.08 +/- 1.87 and 16.19 +/- 9.57 h, respectively. For both the single and multiple dosing of thalidomide, the apparent volume of distribution and half-life were significantly higher for the high-dose group than those for the low-dose group. The higher apparent volume of distribution may be

Related Links

Clinical pharmacokinetics of thalidomide. [Clin Pharmacokinet. 2004]

Plasma pharmacokinetics and urinary excretion of thalidomide after oral dosing in healthy male volunteers. [Drug Metab Dispos. 1989]

Population pharmacokinetics of APOMINE: a meta-analysis in cancer patients and healthy volunteers. [J Clin Pharmacol. 2004]

Thalidomide does not alter estrogen-progesterone hormone single dose pharmacokinetics. [J Clin Pharmacol Ther. 1999]

Pharmacokinetics of dexloxiglumide after administration of single and repeat oral escalating doses in healthy young men. [J Clin Pharmacol Ther. 2002]

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attributable to several factors, such as change in absorption, protein binding, etc. A dose-proportional increase in thalidomide steady-state concentrations was seen after multiple daily dosing of thalidomide.

PMID: 9874712 [PubMed - indexed for MEDLINE]

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